Valproate-induced hyperammonemic encephalopathy with normal liver function

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Hyperammonemic encephalopathy with normal liver function is an uncommon serious adverse effect of valproate therapy. We retrospectively analyzed the case records of 5 patients of epilepsy on valproate with hyperammonemic encephalopathy. Of the 5 patients, 3 were on monotherapy. The mean valproate dose was 1250 mg/day and the duration of therapy ranged between 4 and 90 days. Alteration in the sensorium was the presenting clinical feature. The risk factors included high initial dose (2), long-term valproate therapy (1), and long-term valproate therapy with concomitant topiramate (1). There was good correlation between the fall in serum ammonia levels and clinical improvement. Hyperammonemic encephalopathy should be suspected in patients on valproate with altered sensorium. Response to treatment is rewarding.

Key Words: Valproate, Hyperammonemia, Hyperammonemic encephalopathy

Hyperammonemic encephalopathy is an uncommon serious adverse effect of valproate (2-propylepentanoic acid) therapy. The exact incidence of this serious complication is uncertain. The reported incidence of asymptomatic hyperammonemia in children was 20% and of symptomatic 5%. Valproate-induced hyperammonemic encephalopathy is often seen in association with hepatic dysfunction, but may also rarely occur with normal liver function. Co-medication with other antiepileptic drugs (AEDs) increases the risk of valproate-related hyperammonemia and is a rare complication in patients on valproate monotherapy.

Case Histories

Case records of 5 patients with valproate-induced hyperammonemic encephalopathy were reviewed. The data collected included the type of epilepsy and epilepsy syndrome, the dose and duration of valproate and other AED therapy, neurological features, serum ammonia levels, EEG findings, treatment and outcomes. Diagnostic criteria of hyperammonemic encephalopathy were: treatment with valproate, elevated levels of serum ammonia, and improvement in the clinical features with the decline of serum ammonia on withdrawal or dose adjustment of valproate.

Of the 5 patients, 3 patients were on valproate monotherapy. In the other 2 patients the co-AED medications included topiramate (1), carbamazepine (2), and clobazam (1). The mean duration of valproate therapy was 43.8 days (range 4 – 90 days) and the mean dose was 1250 mg/day (range 750–2000 mg). In both the patients on concomitant AED therapy the dose of valproate was escalated by 500 mg per day before the present illness, before 1 month in one and before 3 months in the other. Alteration in the sensorium was the presenting clinical feature in all the 5 patients. The patient with Sturge-Weber syndrome presented with a history of periodic drowsiness or confusion and occasional vomiting of 3 months duration. Episodic vomiting was one of the seizure semiology in him. Initially this made his parents attribute the drowsiness and confusion to vomiting. They brought the patient only when his drowsiness worsened. The patient had continuous EEG monitoring for 12 hours to exclude non-convulsive status epilepticus (Table 1). All the patients had normal liver enzymes and EEG showed diffuse symmetrical non-rhythmic slowing in the theta to delta range. Carnitine levels were not measured in any of the patients.

Valproate was withheld in all the 5 patients and all patients received lactulose and gut sterilization with ampicillin. There was good correlation between the fall in serum ammonia levels and clinical improvement. None of the patients received carnitine therapy. The dose of valproate was reduced in the patient with JME and also in the patient with intractable temporal lobe epilepsy. In the patient with Sturge-Weber syndrome the drug was withdrawn and topiramate added. All the 3 patients were carefully followed by serum ammonia estimation in the outpatient clinic. Serum ammonia level dropped to the normal range in all the 3 patients. In both the patients with stroke and epilepsy the drug was changed to phenytoin.

Discussion

The clinical presentation of hyperammonemic encephalopathy can be varied and includes irritability, agitation, drowsi-
ness, coma and occasionally these patients may have paradoxical seizures.\textsuperscript{[1],[4]} The other symptoms include loss of appetite, nausea and vomiting.\textsuperscript{[6]} Drowsiness was the presenting feature in all our patients. There was a good correlation between the fall in serum ammonia levels (after VPA withdrawal) and clinical improvement. These features strongly suggest the clinical diagnosis of hyperammonemic encephalopathy.

Hyperammonemia is more common in children\textsuperscript{[2]} and develops within days to weeks of initiation of treatment.\textsuperscript{[3]} Underlying urea cycle enzyme deficiencies predispose to valproate-induced hyperammonemia.\textsuperscript{[7]} Concomitant AED therapy, particularly topiramate, increases the risk.\textsuperscript{[1],[8]-[10]} Other risk factors include underlying liver disease,\textsuperscript{[11]} high initial dose,\textsuperscript{[2]} long-term valproate therapy,\textsuperscript{[12]} co-medication with drugs like salicylates,\textsuperscript{[12]} strict vegetarianism,\textsuperscript{[13]} uretrosigmoidostomy,\textsuperscript{[15]} and disorders associated with reduced albumin synthesis.\textsuperscript{[18]} In our series the probable risk factors were initial high dose of valproate in 2 patients, long-term valproate therapy in 1 patient, and long-term valproate therapy and concomitant topiramate in 1 patient. Three of our patients were on valproate monotherapy. Hyperammonemia is an uncommon adverse effect in patients on valproate monotherapy.\textsuperscript{[11]}

All our patients had normal liver functions. We have not investigated for any underlying urea cycle enzyme abnormalities in our patients. Several possible mechanisms have been described for hyperammonemia in patients on valproate therapy with normal liver functions. Propionate, a metabolite of valproate reduces hepatic N-acety glutamate concentration, which is an obligatory activator of carboxymethyl phosphate synthetase 1 (CPS-1), the first enzyme of the urea cycle. Decline in CPS-1 activity results in defective ammonia utilization and accumulation of ammonia.\textsuperscript{[14]} Another mechanism thought to play a role is reduction of hepatic carnitine levels by valproate. This results in decreased beta-oxidation of fatty acids, which in turn results in reduced levels of Acetyl Co-A. This decrease in Acetyl Co-A ultimately disrupts the urea cycle resulting in ammonia accumulation.\textsuperscript{[15]} The less common mechanism is an increment in the mitochondrial glutamine transport, resulting in increased glutamine uptake by kidneys and release of ammonia.\textsuperscript{[16]}

Hyperammonemia has been described with therapeutic serum valproate levels and there is no direct correlation between serum valproate level and hyperammonemia.\textsuperscript{[17],[18]} However, high serum valproate levels and serum ammonia levels may have a synergistic effect.\textsuperscript{[19]} It is necessary to emphasize that previous satisfactory tolerance to valproate does not preclude the occurrence of hyperammonemic encephalopathy.\textsuperscript{[20]} Serum valproate levels were not estimated in any of our patients and it is not a mandatory criterion. However, in our series there was a good correlation in clinical improvement with the fall in serum ammonia level on valproate withdrawal. Management includes withdrawal or dose adjustment of valproate and appropriately managing the underlying risk factors with excellent outcomes.\textsuperscript{[1],[18]} Carnitine is an essential amino acid necessary in beta-oxidation of fatty acids and energy production in cellular mitochondria. It has been hypothesized that valproic acid may induce a carnitine deficiency in children\textsuperscript{[20]} and also in adults\textsuperscript{[4]} and cause non-specific symptoms of deficiency, hepatotoxicity, and hyperammonemia. Carnitine supplementation has been shown to result in subjective and objective improvements along with increase in carnitine serum concentrations in patients receiving valproic acid. Although carnitine has been well tolerated, future studies are needed to evalu-

### Table 1: Clinical characters and laboratory findings

<table>
<thead>
<tr>
<th>Age/Sex</th>
<th>Epilepsy and epilepsy syndrome</th>
<th>Antiepileptic drugs and daily dose</th>
<th>Duration of therapy</th>
<th>Clinical features and duration</th>
<th>Initial serum ammonia (6 -47μmol/l)</th>
<th>Liver Enzymes AST:0-35u/LALT:0-35u/L</th>
<th>EEG Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>64 M</td>
<td>Ischemic stroke with epilepsy</td>
<td>VPA – 1000 mg</td>
<td>4 days</td>
<td>Drowsiness - 1 day</td>
<td>PreT:133 PostT:12</td>
<td>AST: 22/u/L LALT: 18/u/L</td>
<td>Diffuse symmetric non-rhythmic slowing in theta to delta range</td>
</tr>
<tr>
<td>74 M</td>
<td>Hemorrhagic stroke with epilepsy</td>
<td>VPA – 1000 mg</td>
<td>5 days</td>
<td>Drowsiness – 1 day</td>
<td>PreT:157 PostT:15</td>
<td>AST: 26/u/L LALT: 30/u/L</td>
<td>Diffuse symmetric non-rhythmic slowing in theta to delta range</td>
</tr>
<tr>
<td>14 F</td>
<td>JME</td>
<td>VPA – 750 mg</td>
<td>3 months</td>
<td>Drowsiness – 1 day</td>
<td>PreT:127 PostT:10</td>
<td>AST: 16/u/L LALT: 18/u/L</td>
<td>Diffuse symmetric non-rhythmic slowing in theta to delta range</td>
</tr>
<tr>
<td>17 F</td>
<td>Intractable temporal lobe epilepsy</td>
<td>VPA–1500 mg</td>
<td>1 month</td>
<td>Vomiting, exhaustion, drowsiness -3 days</td>
<td>PreT:149 PostT:15</td>
<td>AST: 30/u/L LALT: 30/u/L</td>
<td>Diffuse symmetric non-rhythmic slowing in theta to delta range</td>
</tr>
</tbody>
</table>

VPA: Valproate, CBZ: Carbamazepine, TPM: Topiramate, CZM: Clobazam; JME: Juvenile myoclonic epilepsy; PreT: Pre-treatment; PostT: Post-treatment

*The dose of valproate was escalated from 1000 mg to 1500 mg 1 month before the present illness.

**This patient had continuous EEG recording for 12 hours to exclude non-convulsive status epilepticus.
ate the efficacy of prophylactic carnitine supplementation for the prevention of hepatotoxicity.[21] We have not measured serum carnitine levels or given carnitine to any of our patients.

Hyperammonemia is a serious adverse effect of valproate therapy and may be potentially life-threatening in the presence of underlying hepatic dysfunction and enzyme deficiency disorders. The diagnosis of hyperammonemic encephalopathy should be suspected in any patient on valproate therapy with altered sensorium. Response to therapy is rewarding.

References


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